Combined Monitoring Board

Reviews Multi-site Interventional Health Service Studies

GUIDELINES

Modified September, 2005

VA Health Services Research & Development Service

Introduction

The requirement for data and safety monitoring of clinical trials is addressed in VHA Handbook 1200.5, paragraph 7. A. (6). VA's policy on data and safety monitoring is consistent with that of the Department of Health and Human Services which states that: "The establishment of data and safety monitoring boards is required for multi-site clinical trials involving interventions that entail potential risk to the participants." (NIH Policy for Data and Safety Monitoring, June 10, 1998).

The purpose of this manual is to describe practices and procedures for the organization and function of the Combined Monitoring Board (CoMB) to review Health Services Research & Development (HSR&D) multi-site intervention studies in the Veterans Health Administration (VHA). Multi-site studies are those in which investigators from two or more VA (or non-VA, as appropriate) medical centers with separate IRBs agree to study collectively a selected problem in a uniform manner, using a common protocol with central coordination.

Although multi-site studies are generally not appropriate for the early development and refinement of new preventive or therapeutic techniques, they are particularly advantageous in the later stages of evaluation of safety, treatment effectiveness, and cost effectiveness of health care interventions that have already had the necessary preliminary trials in humans. Clinical trials and health services research studies of this type, as well as some epidemiological studies, can benefit from a multicenter approach that facilitates the accumulation of patient samples that are:

- Sufficiently large to provide a definitive answer to the research questions. For medical conditions that are relatively rare, multi-site studies may be the only feasible approach, but even in more common conditions, pooling the observations made in several facilities can accumulate knowledge more rapidly.

- Sufficiently diverse to permit broad generalizations of results.

The large number of medical centers within the VA presents an ideal environment for conducting multi-center studies. The VA has a large and relatively uniform patient base; this is especially appropriate for research that addresses medical problems and diseases prevalent in the veteran population. These characteristics facilitate the conduct of multi-center studies that require strict adherence to a common protocol. In this setting, it is more likely that the essential patient follow-up will be completed.

Purpose of the Combined Monitoring Board (CoMB)

The Combined Monitoring Board (CoMB) provides a continuing critical and unbiased evaluation of the study's progress and the analysis plan, consistent with the best contemporary health services research practice. It does not initially evaluate the scientific merit or methodology of the study, nor does it subsequently participate in the

study's conduct, monitor the budget, or review and approve subprotocols; these functions are performed by the HSR&D Service in VACO or by other committees.

The CoMB will perform many of the functions of a Data and Safety Monitoring Board. The major responsibilities of the CoMB are:

- To assess the performance of each participating center and make appropriate recommendations regarding continuation, probationary status, or termination.

- To consider whether the study should continue. Inherent in this question are considerations such as patient accrual, overall study progress (timeline and follow-up participation), adverse effects and patient safety, treatment effectiveness/futility, and proper monitoring and reporting by the study team.

- To review the analysis plans and make recommendations for additions or changes to the plan.

After a study is approved and funded, the HSR&D Director will notify the Palo Alto Cooperative Studies Program Coordinating Center (CSPCC) if the study is a multi-site intervention posing some potential risk to participants and should be reviewed on an annual basis by the CoMB. The CSPCC will then contact the Study Chairperson to provide information on the reviews.

Briefing the CoMB about the Analysis Plan

To aid the CoMB to fulfill its responsibility of reviewing the data analysis plan, the Study Chair (i.e., Principal Investigator) will submit a 3 – 5 page description of the analysis plan of the study to HSR&D within 30 days after being notified of study funding. HSR&D will forward the report to the CoMB.

The description of the analytic plan should summarize all of the statistical analyses for the primary, and important secondary, hypotheses or research questions specified in the original proposal. While there may have been a data analysis plan included with the original proposal, the Study Chair should assure that there is a discussion of each of the following points applicable to the study:

- The rationale for the study sample size
- The method of randomization (describing any stratification and blocking techniques)
- Plans for and specification of the purpose of any interim looks at the data (with regards to stopping rules for superiority, futility, or sample size re-estimation)
- Methods for handling missing data points and subject dropouts
- Definitions of covariates to be included in adjustment models
- Methods for dealing with data transformations
- Definitions of the analytical sets (i.e. intent-to-treat, per-protocol, and any other analytical subsets)

Committee members, and especially the biostatisticians on the Committee, will review and comment on the character and definition of response variables, sample size, and plans for measurement, data collection, frequency of observations, data processing and analysis, as well as any other relevant features.

CoMB Reviews of Ongoing Studies

The CoMB meets face to face once a year in January/February in the San Francisco area.

All HSR&D multi-site intervention studies that entail potential risk to participants are reviewed annually by the CoMB. The initial progress review will take place as scheduled by HSR&D staff in VACO. If by the time of the initial review, patient intake has already begun, then the review will be face to face with the CoMB; after any face-to-face meeting, subsequent reviews may be by teleconference, at the discretion of the board. These reviews will be based on a progress report prepared by the Study Chairperson. The deadline for this report is generally about three weeks prior to the scheduled meeting, and attendees will be notified in plenty of time in advance.

If at the time of the initial progress review, patient intake has either not begun or has been underway for a relatively short time, at the Board's discretion, the review may be accomplished by teleconference, during which the Study Chairperson will brief the CoMB concerning the study design and study progress. Subsequent annual reviews will be conducted face to face with the CoMB.

Progress Report of Ongoing Studies

For the annual review of multi-site HSR&D studies, whether in-person or by teleconference, the Study Chairperson will be responsible for submitting the progress report to the CSPCC in the following format:

- Study Chairperson's **Summary of Progress Cover Letter**. The Study Chairperson shall prepare a short letter (maximum 5 pages) addressed to the CoMB covering study progress and performance. This letter should include a history of the study to date, including current study stage (pre-initiation of recruitment, recruitment & follow-up, follow-up only, post-data collection analysis only) and a statement of the current status. The latter includes the number of patients entered into the study and a comparison with the projected number; losses to the study and a statement of when and why these occurred; comparison of recruitment results to date with study objectives; and estimates of the prospects of success. The letter should conclude with a persuasive paragraph explaining why the study should be continued (if that is the case).

- Table of Contents.

- Executive Summary or Abstract of the Study.

- A **GANTT** chart (by specific calendar year or specific fiscal year)

- A **chronology** of major events that have occurred (e.g. start of funding, start of patient recruitment, study meetings, changes in participating sites, important protocol changes, scheduled end of funding)

- Tabular material: Each table or set of tables should be interspersed with narrative sections. These narrative summaries should point out salient features and emphasize areas of special interest. They should serve the reader as a 'road map' guide to the tables. The tables should present data on the following areas:
    - **Enrollment** – number of patients entered into the study (by time and site) in comparison with the projected number. A graph comparing actual recruitment with projected recruitment over time is suggested.
    - **Baseline comparison** of relevant characteristics of study groups
    - **Recruitment and retention flow diagram (**ref: **JAMA)**
    - **Patient Retention**– deaths, losses to follow-up, withdrawals, etc., by site
    - **Patient Safety** – Adverse Events (AE) and Serious Adverse Events (SAE), including changes of therapy or intervention due to failure or toxicity. The AE and SAE tables should be presented by group, with the groups unblended, i.e., identified solely as Group A, Group B, etc.

      Adverse Event (AE) – Any untoward medical occurrence experienced by a patient after the patient is enrolled in the study. A causal relationship to the study intervention is not necessarily implied, and therefore an AE can be any unfavorable or unintended sign (including an abnormal laboratory finding), symptom, or disease.

      Serious Adverse Event (SAE) - Any AE that poses a serious threat to a study patient's health. As defined by the FDA, this includes:
      1) Any fatal event
      2) Any life-threatening experience
      3) Any event which requires or prolongs a hospital stay
      4) Any event which is permanently disabling or incapacitating
      5) Any congenital anomaly/birth defect
      6) Any other condition that may jeopardize the patient and require medical or surgical treatment to avoid one of the above outcomes

    - **Effectiveness** - Aggregated outcome data, including a comparison of the overall outcome-event rates with the rate predicted in the original protocol. The CoMB prefers the presentation of aggregate data, but at their discretion, the CoMB, after reviewing the aggregated results, may request outcome data by blinded treatment assignment (group A vs. group B), or, in unusual circumstances, unblinded outcome data. To keep the Study Chair from being influenced by the interim results, if requested,

these sections should be completed by the Study Biostatistician and mailed to the CSPCC separately.
    - Reconsideration of the power/sample size issues may be necessary. In the case of a request for extension of patient intake or follow-up duration, this report should also contain a justification for the request. When investigators request an extension or if there is any problem with the conduct of the trial, the calculation of conditional power must be provided to the CoMB.

- Appendix
    - Previous CoMB feedback reports, if any. The CoMB feedback report is generated to reflect the CoMB review and approval of the study to continue, and it is signed by the CoMB Chairperson.
    - (Possibly updated) 25 page narrative section from the approved protocol. (Do not include entire protocol.)
    - Informed Consent Form(s)
    - Other supplemental material (optional)

Once the CSPCC receives the report, it is reviewed to ensure that all the required information is included. Copies of the report are then sent to the CoMB members.

Organization of the CoMB Review

The CoMB reviews ongoing multi-site HSR&D studies and makes recommendations to the HSR&D Director.

1. Composition of the Board

The HSR&D Director appoints members of the CoMB. CoMB members are highly qualified by background, training, experience, and knowledge in relevant disciplines.

- *Regular* Voting Members: Two HSR&D Researchers, two Biostatisticians, a Health Economist, and an Epidemiologist. These members will serve three-year terms, with not less than one year between terms. The terms will be staggered to provide partial change in membership on an annual basis.

- *Rotating* Voting Members: Study Chairpersons of ongoing studies will serve on one Board during the course of their study. For each day of a CoMB meeting, two study chairpersons will be selected to sit on the Board, and during this day, they will have all the authority and privileges of the regular members.

- *Ex-officio* Non-voting Members: The HSR&D program representative(s) and the Palo Alto CSPCC representatives.

The HSR&D Director nominates the Chairperson of the CoMB. The responsibilities of the Chairperson are to conduct the meeting and to summarize the deliberations of the Committee.

Board members who participated in the planning of the study or who play a continuing key role in the study should recuse themselves when that study is under review.

The HSR&D Service will pay the travel expenses for CoMB members and one Study Chairperson from each study to attend the meeting. Non-VA CoMB members will be paid an honorarium. Meetings of the CoMB are closed meetings so that additional attendees, such as pharmaceutical representatives, may not attend these meetings unless specifically invited by the CoMB for the purpose of clarifying specific issues.

2. The CoMB Review Process

A Study Chairperson will be funded to appear before the CoMB. At the meeting, the Study Chairperson will be asked to make an opening statement not to exceed fifteen minutes. The statement should include the background of the study, a brief summary of the study design, the patient recruitment and retention record, safety issues, and any interim monitoring. In making the opening statement, the Study Chairperson may make reference to material in the study's progress report, but there will be no access to audio-visual equipment, e.g., slide projector, overhead projector, PowerPoint presentation, etc. Handouts should be kept to a minimum.

After the formal statement, 45 minutes will be allotted for a conversation between the CoMB and the Study Chairperson, to focus on questions based on the written progress report that the CoMB has been able to review prior to the meeting. Committee reviewers are asked to comment on the plan of investigation, the patient recruitment and retention performance, study progress, the analysis plan, and any other pertinent features of the report. The biostatistical reviewer is asked to comment also on the character and definition of response variables, measurement, data collection, frequency of observations, sample size, progress on data processing and analysis, and any other relevant features.

After the discussion, the Study Chairperson will be excused for the CoMB Executive Session of about 30 minutes. The HSR&D and the CSPCC program representatives will remain as non-voting members. The Executive Session will include a consideration of a formal motion to continue the study, the language of the CoMB report to IRBs, and any recommendation for changes in the conduct of the study.

3. CoMB Recommendations

Generally one of three actions is taken:

- Unconditional approval. The study is approved to continue.

- Conditional approval. The Committee approves the study to continue, but approval is contingent on specific recommended modifications.

- Close the study. The study should be terminated.

Study Chairs who attend the meeting will be informed of the CoMB recommendation(s) immediately after the Executive Session; those attending by teleconference will have an opportunity to be informed of the CoMB recommendation(s) within 10 working days of the close of the CoMB meeting. The recommendation is forwarded to the HSR&D Director, who will issue a formal report.

In addition to chairing each meeting, the Chairperson of the CoMB will be responsible to prepare a brief feedback report of each study review session. The feedback report states those actions that the Board believes are necessary or highly desirable. These are phrased as recommendations to the HSR&D Director. The CoMB may also make suggestions that are not intended to be binding but are to be considered and discussed by the study representatives. After the HSR&D Director issues the report, the Study Chairperson will be asked to submit a response to indicate how the recommendations will be implemented.

Along with the CoMB feedback report, the CoMB Chairperson will prepare a short report that the Study Chairperson may distribute to the Human Subject Subcommittees/IRBs of the participating sites, informing them of any safety issues in the study. Since the Human Subject Subcommittees/IRBs will not have access to blinded data results, the report will provide them some assurance that the CoMB is monitoring the safety of study patients and will make them aware of any safety issues. The report needs to be worded such that blinded study results are not revealed unless absolutely necessary.

The CoMB reports are provided to the HSR&D Director who determines the action needed for each report, transmits the report with a cover letter of the action to the appropriate Hospital Director with a copy to the Associate Chief for Research and the Principal Investigator of the study.

"Midyear" CoMB Review

At mid-year between annual reviews, all Study Chairs should submit a (4-6 page) Six Month progress report which covers:

- Study Chairperson's **Summary of Progress Cover Letter (**at most 1 page). The Study Chairperson should prepare a letter covering study

progress, performance, and important protocol modifications since the last review of the study

- Recruitment table or graph showing actual vs expected recruitment rates for the entire study and by site
- Completeness of follow-up
- Status of data collection and data processing
- Safety: SAEs and AEs classified by group (A vs B, i.e., blinded), cumulative and for the past 6 months.

The document will be sent to the CSPCC to be reviewed by the CoMB Chair and HSR&D Representative. Possible actions include acceptance without comment, sharing the document with the entire CoMB for an email vote, or requesting the Study Chair to present the report at a teleconference of the entire CoMB.